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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,667	07/10/2002	Philipp Holliger	109312.122US1	9374

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EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,667	HOLLIGER ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *5-8 and 10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9 and 14-27* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☒ Claim(s) *1-27* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The previous Restriction requirement contained a typographical error, inadvertently including claims 10-13 with Group I and claims 14-27 with Group II. In order to clarify the record, Applicant was informed in an Interview (see attached) that the previous Restriction requirement would be corrected to properly indicate the members of the Groups.

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-4, 9, 14-27, drawn to a method of detecting a protein-nucleic acid interaction using a hybrid protein comprising a σ54 activator domain and a nucleic acid binding domain.

Group II, claim(s) 5-8 and 10-13, drawn to a method of detecting a protein-protein interaction using a first and second hybrid protein, wherein one hybrid protein comprises a constitutively active σ54 activator domain and the other hybrid protein comprises a nucleic acid binding domain.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Group I is the fusion of a σ54 activator domain and a nucleic acid binding domain, which can then be used to detect the ability of the binding domain to either interact with or bend a nucleic acid.

The special technical feature of Group II is the use of two different fusion proteins, one comprising a σ54 activator domain fused to a first protein of interest and the other comprising a nucleic acid binding domain fused to a second protein of interest, wherein the two fusion

proteins can be used to detect whether the two proteins of interest interact. This special technical feature is different from the special technical feature of Group I because the methods use functionally and structurally different fusion proteins, and are furthermore directed to identifying different types of biochemical interactions (i.e., protein-nucleic acid in Group I versus protein-protein interactions in Group II). Because the two groups are associated with different special technical features, the inventions are properly restricted as being drawn to different inventive methods.

In response to the previous Office Action, Applicant elected Group I with traverse. This election was confirmed in a telephone interview with Belinda Lew, Ph.D. on June 21, 2005 (see attached).

Applicant's election with traverse of Group I (claims 1-4, 9 and 14-27) in the reply filed on December 1, 2004 (and confirmed on June 21, 2005) is acknowledged. The traversal is on the ground(s) that inventions of Groups I and II are closely related, and that a search of the prior art of the methods of Group I would necessarily encompass a search of the prior art of the methods of Group II because both methods use "one or more hybrid proteins" (see for example the second paragraph of the second page of Applicant's response to the Restriction requirement).

This is not found persuasive because the Groups were restricted under the practice of lack of unity, this case being a national stage entry of an international application. Under lack of unity standards, inventions must be linked by a common special technical feature in order for the inventions to be considered non-restrictable. In the restriction requirement, the Office has established that Groups I and II have different special technical features, drawn to the biochemical nature of the elements (i.e., the different types of fusion proteins) used in each group. Because Applicant has not provided any reason why the special technical features set forth in the previous restriction requirement are not proper, the Office can only consider that the

Groups indeed have different special technical features, and are therefore properly restrictable. As such, the restriction requirement is considered proper, and is maintained.

Claims 1-27 are pending in the instant application. Claims 5-8 and 10-13 are withdrawn as being drawn to a non-elected invention. Claims 1-4, 9 and 14-27 are under examination in the instant application.

Information Disclosure Statement

The information disclosure statement filed March 8, 2002 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to this Office Action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

The disclosure is objected to because of the following informalities: the current Abstract is a copy of the first page of a corresponding WO document. The Office no longer accepts the

first page of a WO document as an Abstract for publication reasons. Applicant is required to supply a new Abstract on a separate sheet.

Additionally, the first page of the claims is objected to for simply reciting the term "Claims" at the top of the page. In order for the claims to be in proper format, the first line of the claims should read in sentence format. For example, the phrases "What is claimed is:" or "We claim:" would be permissible substitutes.

Appropriate correction is required.

Claim Objections

Claim 4 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be recited in the alternative. See MPEP § 608.01(n). In the instant case, claim 4 is dependent on claim 1 *and* claim 2 *and* claim 3, which is not the recitation of multiple claims in the alternative. Accordingly, claim 4 not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a method for detecting a protein-nucleic acid interaction by using "one or more hybrid sigma-54 activator proteins comprising...a constitutively active sigma-54 transcription activating domain." The claims read on a broad genus of "constitutively active sigma-54 transcriptional activation domains" that can be used in the claimed method.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims a "constitutively active sigma-54 transcriptional activation domain" by function only, without any disclosed or known correlation between the elements and their function. Specifically, the skilled artisan must be able to envision the chemical structure of any "constitutively active sigma-54 transcriptional activation domain," which must necessarily have the ability to activate transcription without regulation. The specification only provides teachings regarding two particular "constitutively active sigma-54 transcriptional activation domains," the NifA and PspF transcriptional activators (see for example page 13, lines 11-23); each of these proteins requires the elimination of a second protein (i.e., a negative regulator) in order to convert them into "constitutive activators." The specification does not teach any other structure-function relationship that would allow the skilled artisan to envision what mutations could be

made to a sigma-54 transcriptional activation domain to convert it from a regulated activator into a constitutive/unregulated activator. Indeed, the specification merely suggests that the skilled artisan could convert a sigma-54 activation domain into a constitutively active domain by "removal of the N-terminal regulatory domain or by appropriate mutation" (see for example page 13, lines 25-26), without disclosing or suggesting what mutations are necessarily appropriate for the conversion of a regulated sigma-54 transcriptional activator into a constitutive activator. Thus, the skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification without the disclosure of mutations to the activator that will necessarily result in the conversion of an activator to a state of constitutive activation.

The prior art does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. Indeed, a review by Shingler (*Mol. Micro.* **19**: 409-416, 1996; see entire document) indicates that there are multiple mechanisms of regulation for sigma-54 activator proteins (see for example page 411, right column to page 413, right column), including protein-protein interaction, phosphorylation and direct activation by secondary elements (such as aromatic amino acids, in the case of DmpR). Thus, in order to produce constitutive activators, the skilled artisan would need to understand both the mechanism by which a particular factor is activated, as well as how to produce that activation signal constitutively. For example, if the activation is by de-repression, the skilled artisan would be required to envision which mutations would prevent the binding of an inhibitory factor, thus producing a constitutive activator. Similarly, if activation is by phosphorylation or by the binding of a co-factor, the skilled artisan would be required to envision which mutations would mimic the phosphorylated or substrate-bound state in order to produce a constitutive activator.

However, Shingler does not provide a distinct structural feature that, when mutated, will necessarily produce constitutive activators. Thus, the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

The specification describes a single mechanism for producing constitutive sigma-54 activators, by deletion of an inhibitory factor, and provides two specific examples of this mechanism (NifA and PspF) (see for example page 13, lines 11-23). However, Shingler teaches that there are clearly multiple regulatory mechanisms for sigma-54 activators (see for example pages 411-413). Unfortunately, neither Shingler nor the instant specification further the understanding of what mutations can mimic the activated state of the broad genus of sigma-54 transcriptional activators. For instance, there is no description of mutants that can mimic the phosphorylated or substrate-bound state of an activator, such that the activator will become constitutive. As a result, the skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art and/or the instant specification to produce the broad genus of "constitutively active sigma-54 transcriptional activation domains" that are necessary components of the invention. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method using NifA and PspF as constitutive sigma-54 activators, does not reasonably provide enablement for a method of using any sigma-54 constitutive activator. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The invention is a method for detecting protein-nucleic acid interactions, and requires the use of a "constitutively active sigma-54 activation domain." In order to practice the inventions, the skilled artisan would need to know how to make any "constitutively active sigma-54 activation domain." Thus, the skilled artisan would have to be apprised of what mutations, either to the activator itself, or to a negative or positive regulator of the activator, will necessarily result in the constitutive activation of the factor/domain. As set forth above, Applicant has not provided a Written Description of such activators, thus making it impossible to make the broad genus of activators required for practicing the full scope of the invention.

Breadth of the claims. The claims are very broad, encompassing the use of a large genus of "constitutively active sigma-54 transcriptional activation domains." The scope includes not only the use of factors that can be made constitutively active by the deletion of a negative regulatory

factor (such as NifA and PspF), but also of factors that can presumably be made constitutively active by other mechanisms (such as mimicking a phosphorylation state).

Number of working examples and Guidance provided by applicant. The instant specification provides two examples of "constitutively active sigma-54 transcriptional activation domains," NifA and PspF. The constitutive activation of both factors is achieved by the deletion of negative regulators of these activators (see for example page 13, lines 11-23 of the instant specification). The instant specification further states that other constitutive activators can be produced by the "removal of the N-terminal regulatory domain or by appropriate mutation" (see for example page 13, lines 25-26). However, the instant specification does not disclose any teaching of mutations that will necessarily result in the conversion of a regulated sigma-54 transcriptional activator into a constitutive activator.

State of the art. A review by Shingler (as recited above) indicates that there are numerous regulatory mechanisms for sigma-54 transcriptional activators (see for example pages 411-413). These mechanisms include protein-protein interaction, phosphorylation state and binding of co-factors. However, Shingler does not provide a teaching as to what mutations in these sigma-54 activators will necessarily result in their conversion from regulated factors to constitutively active factors; Shingler simply provides evidence that there are multiple ways to regulate sigma-54 activators, thereby implying that there are multiple ways to constitutively activate these factors. Similarly, the remainder of the art does not clearly disclose a mechanism for making constitutive activators. Thus, the state of the art does not appear to remedy the deficiency of the instant specification regarding the ability to make a sigma-54 activation domain that is not regulated in its normal manner.

Unpredictability of the art and Amount of experimentation required. The invention is highly unpredictable because the skilled artisan is not aware of what mutations in what particular sigma-54 transcriptional activators will necessarily result in the production of constitutive activators. Neither the instant specification nor the state of the art provides sufficient guidance on how to make such activators, which are the key factors for performing the method as claimed. Indeed, the state of the art indicates that there are multiple mechanisms for regulating the activity of a sigma-54 transcription factor, but the instant specification merely teaches how to affect the regulation of two specific factors, NifA and PspF via single mechanism. In order to practice the full scope of the instantly claimed method, the skilled artisan would be required to empirically determine how to produce other "constitutively active sigma-54 transcriptional activation domains," many of which will be regulated by different mechanisms than those that regulate NifA and PspF; this requires undue and unpredictable trial and error experimentation. The skilled artisan would essentially be required to perform an inventive step (making the experimentation undue) by determining how to make a large scope of "constitutively active sigma-54 transcriptional activation domains," if the full scope can even be made (make the experimentation unpredictable). As such, Applicant has not satisfied the enablement requirement for the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 14-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 14-27 recite an acronym "IHF" without defining the acronym. In the absence of an indication as to the meaning of the acronym, the skilled artisan would not be apprised of the metes and bounds of the claim.

Claims 14-17 and 20-27 recite the use of accession numbers, meant to represent sequences. It is well established that the sequences represented by accession numbers are subject to change through updates and corrections. Because these sequences are subject to change, the metes and bounds of the indicated claims are indefinite because they are also subject to change. If Applicant wishes to recite specific sequences as a means of limiting their claims, they are required to submit the specific sequences in the specification and the claims.

Claims 16, 17 and 20-27 recite the limitation "the hybrid sigma-54 transcriptional activator " in reference to claim 14. However, there is no recitation of a "hybrid sigma-54 transcriptional activator " in claim 14 (or its dependent claim 9). Thus, there is insufficient antecedent basis for this limitation in the claim, making it unclear if the independent claim(s) is supposed to include a limitation where the activator is a hybrid, or if the dependent claim is not meant to be limited to a hybrid.

Regarding claims 22-27, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). It would be remedial to eliminate the term "such as " from the claim, or to

submit additional dependent claims that specifically recite the exemplified embodiments as limitations.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JAMES KETTER
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